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Integrated Ethnomedicine Study in Silico of Medicinal Plants for Hypertension

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Abstract

This study aims to discover a new formula from natural ingredients that are effective as antihypertensive agents through ethnomedicine research and in silico testing. The study was conducted at the Beringharjo Jamu Market in Yogyakarta by identifying the three most commonly used plants by vendors: Sambiloto (Andrographis paniculata), Akar Pule Pandak (Rauvolfia serpentina), and Seledri (Apium graveolens). Ethnomedicine studies used quantitative parameters such as Relative Frequency of Citation (RFC), Use Value (UV), Fidelity Level (FL), and Informant Consensus Factor (ICF). Subsequently, in silico tests were conducted with a network pharmacology and molecular docking approach to analyze protein-target interactions and test the potential of active compounds from these three plants. The results showed that Sambiloto had the best affinity through the compound Andrographolide with an affinity value of -561 kcal/mol. This study confirms that the three plants have the potential to contain key active ingredients for hypertension therapy using the Ethnomedicine Driven Reversal Approach System (EDRAS), which has proven to be effective and efficient.

Introduction

The Basic Health Research (Riskesdas) data from 2018 shows that the prevalence of hypertension diagnoses in Indonesia increased from 25.8% in 2013 to 34.1% in 2018 (Allen et al., 2020). Indonesia is a country rich in biodiversity, known to have 20,000 types of medicinal plants, of which 1,000 have been documented, and 300 species have been utilized as medicinal plants (Kasmawati et al., 2019). The Beringharjo jamu market holds indigenous knowledge about medicinal plants, which has been preserved among jamu vendors, including medicinal plants for hypertension. Through an ethnomedicine study at the Beringharjo jamu market, three medicinal plants most commonly used for hypertension will be identified. The data on these three selected medicinal plants is sourced from the ethnomedicine study using four quantitative analysis parameters: RFC (Relative Frequency of Citation), UV (Use Value), FL (Fidelity Level), and ICF (Informant Consensus Factor) (Siska & Kustiawan, 2022; Remaja et al., 2017).

Efforts are needed to discover a new medicinal formula for hypertension from natural ingredients that are proven effective (empirical proof) and efficient (in terms of time and cost). The Ethnomedicine Driven Reversal Approach System (EDRAS) is a method for discovering a new medicinal formula from natural ingredients that is effective and efficient in terms of time and cost through ethnomedicine studies at the Beringharjo Jamu Market, which has indigenous knowledge integrated with in silico testing (network pharmacology and molecular docking).

The research problem being investigated includes: 1) What are the three most commonly used medicinal plants for antihypertensive purposes by jamu vendors at the Beringharjo Market, based on the analysis of RFC, UV, FL, and ICF quantitative parameters? 2) What are the

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relevant disease genes and pathways that match between the compounds and the disease genes? 3) What is the lowest binding energy and the synergistic effect of the main active ingredients from the three selected medicinal plants through in silico testing?

The urgency of this research lies in the need to find a new formula for antihypertensive drugs (as hypertension has a high prevalence) that is both effective and efficient in terms of time and cost.

The goal of the research is to find a new antihypertensive formula from natural ingredients that is proven to be effective and obtained efficiently (in terms of time and cost) through in silico testing (network pharmacology and molecular docking) based on ethnomedicine in the form of indigenous knowledge at the Beringharjo Jamu Market in Yogyakarta.

Methods

This research uses a mixed-method approach: both non-experimental and experimental, as well as quantitative and qualitative. The ethnomedicine study was conducted at the Beringharjo Jamu Market, focusing on three medicinal plant species identified based on questionnaires as the most frequently used for hypertension treatment by vendors at the market. Quantitative testing was conducted using four parameters: Relative Frequency of Citation (RFC), Use Value (UV), Fidelity Level (FL), and Informant Consensus Factor (ICF). The active compounds from the three selected medicinal plants were confirmed through in silico testing (network pharmacology and molecular docking) to determine the strongest ligand-receptor binding energy.

The molecular docking method in this study was used to evaluate ligand-receptor interactions through computational simulations to predict binding affinities. This process was conducted using software such as Autodock and Discovery Studio, which involved removing water molecules, separating ligand and receptor structures, adding polar hydrogen atoms, and visualizing molecular structures. The target protein was obtained from the Protein Data Bank (PDB) with PDB ID 4C2P, and the native ligand used for comparison was X8Z-Captopril.

Test ligands from the three selected plants were then docked against the receptor to evaluate the binding affinities of each. The goal of this method is to find the lowest binding energy, which represents the best interaction—where lower binding energy indicates a stronger potential for ligand-receptor binding. This process was conducted to obtain the best affinity of each compound and compare it to the affinity of the native ligand.

Ethnomedicine Study

The ethnomedicine study was conducted to gather data on the three most commonly used medicinal plants for hypertension by vendors at the Beringharjo Jamu Market. The method involved collecting data through a validated questionnaire, administered to vendors at the market. Quantitative analysis of the ethnomedicine data in this study utilized four parameters: Relative Frequency of Citation (RFC), Use Value (UV), Fidelity Level (FL), and Informant Consensus Factor (ICF). The final outcome was to obtain data on the three most commonly used medicinal plant species for hypertension.

Radar Analysis

The percentage composition of active compounds was determined through radar analysis. This was achieved by conducting a literature review on *Andrographis paniculata*, *Rauvolfia serpentina*, and *Apium graveolens*, focusing on six parameters: total flavonoids, total

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polyphenols, ACE inhibitors, antioxidants, systolic reduction, and diastolic reduction. These six parameters are involved in hypertension mechanisms.

Network Pharmacology

Data analysis was conducted using computational methods and online applications such as PubChem, Swiss Target Prediction, GeneCards, Venny, and String-DB. The concept involved creating a network from the selected database based on the LCMS results for the active compounds from the three chosen medicinal plants. The names of these compounds were entered into PubChem to obtain the CID and Canonical Smile for each compound. Targets for these compounds were obtained by entering the Smile code into the Swiss Target Prediction database. Hypertension-related targets were obtained through the GeneCards database. Venny 2.1.0 was used to identify overlaps between compound targets (from Swiss Target Prediction) and hypertension targets (from GeneCards). The protein-protein interaction network was visualized using the String database, enabling the identification of relevant disease genes and pathways.

Molecular Docking

Molecular docking is a computational simulation used to predict the interaction between a drug/ligand and a receptor/protein. The goal is to find the interaction with the lowest binding energy, as this represents the best interaction. This study used Autodock and Discovery Studio software to remove water molecules, separate ligand and receptor structures, add polar hydrogen atoms, and create visualizations. The target protein was obtained from the Protein Data Bank with PDB ID 4C2P, and the native ligand used for comparison was X8Z-Captopril. The test ligands from the three selected plants were subjected to molecular docking to evaluate their binding affinities.

Results and Discussion

Ethnomedicine Study

Beringharjo Jamu Market, as the center of indigenous knowledge collection, provided information on the three most commonly used plants by vendors through a validated questionnaire. The analysis using RFC, UV, FL, and ICF revealed that Sambiloto (Andrographis paniculata), Akar Pule Pandak (Rauvolfia serpentina), and Seledri (Apium graveolens) were the top three plants used for hypertension treatment.

***Relative* i*Of* (RFC) (MENTIONS)**

FC : Citation Frequency (%)

N : Total respondent informants who said the name of the plant and its use

Q : Number of respondents who filled out the questionnaire

Table 1. *Relative Frequency of Citation*

No	Plant Name	Spesies	N	T	FC = (N/T) X 100
1	Sambiloto	*Andrographis paniculata*	11	44	25,00
2	Akar Pule Pandak	*Rauvolfia serpentina*	9	44	20,45
3	Seledri	*Apium graveolens L.*	6	44	13,64
4	Rosela	*Hibiscus sabdariffa*	5	44	11,36
5	Mengkudu	*Morinda citrifolia*	5	44	11,36
6	Biji Mahoni	*Swietenia macrophylla*	4	44	9,09
7	Ciplukan	*Physalis angulata*	4	44	9,09

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8	Timun	*Cucumidis Folium*	4	44	9,09
9	Daun Salam	*Syzygium polyanthum*	3	44	6,82
10	Kelor	*Moringa oleifera L*	3	44	6,82
11	Kayu Manis	*Cinnamomum zeylanicum*	3	44	6,82
12	Bawang Lanang	*Allium Sativus L.*	3	44	6,82
13	Jipang	*Sechium edule*	3	44	6,82
14	Mahkota dewa	*Phaleria macrocarpa*	2	44	4,55
15	Daun Sirsak	*Annona muricata L*	2	44	4,55
16	Kunyit	*Curcuma longa L.*	2	44	4,55
17	Jahe	*Zingiber officinale*	2	44	4,55
18	Jahe Merah	*Zingiber officanale var rubrum*	2	44	4,55
19	Brotowali	*Tinospora cordifolia*	2	44	4,55
20	Temu Mangga	*Curcuma Amada.*	2	44	4,55
21	Sereh	*Cymbopogon citratus*	1	44	2,27
22	Daun Kenikir	*Cosmos caudatus*	1	44	2,27
23	Daun Meniran	*Phyllanthus urinaria L.*	1	44	2,27
24	Ketumbar	*Coriandrum sativum*	1	44	2,27
25	Temu Ireng	*Curcuma aeruginosa*	1	44	2,27
26	Kumis Kucing	*Orthosiphon aristatus*	1	44	2,27
27	Pegagan	*Centella asiatica*	1	44	2,27
28	Pare	*Momordica charantia*	1	44	2,27
29	Daun Pepaya	*Carica papaya L.*	1	44	2,27
30	Semangka	*Citrullus lanatus*	1	44	2,27
31	Teh Hijau	*Camellia Sinensis*	1	44	2,27
32	Lidah Buaya	*Aloe vera*	1	44	2,27
33	Bidara Laut	*Strychnos lucida*	1	44	2,27
34	Manggis	*Garcinia mangostana L*	1	44	2,27
35	Bawang Dayak	*Eleutherine palmifolia*	1	44	2,27
36	Melon	*Cucumis melo L.*	1	44	2,27
37	Cincau	*Cyclea barbata*	1	44	2,27
38	Labu Siam	*Sicyos edulis*	1	44	2,27
39	Adas Pulo Waras	*Foeniculum vulgare*	1	44	2,27
40	Widara Laut	*Strychnos lucida*	1	44	2,27
41	Daun Sambung Nyawa	*Gynura procumbens*	1	44	2,27
42	Bawang Putih	*Allium sativum*	1	44	2,27
43	Belimbing Kuning	*Averrhoa carambola L*	1	44	2,27

***Use* i*Value* (UV)**

UV : Usability value of plant species

∑U : Number of respondents who understood or understood the species

N : Total number of respondents or informants

Table 1. *Use Value* (UV)

No	Plant Name	Spesies	∑U	n	UV = ∑UI/n
1	Sambiloto	*Andrographis paniculata*	21	44	0,48
2	Akar Pule Pandak	*Rauvolfia serpentina*	14	44	0,32
3	Seledri	*Apium graveolens L.*	12	44	0,27

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4	Daun Salam	*Syzygium polyanthum*	8	44	0,18
5	Ciplukan	*Physalis angulata*	8	44	0,18
6	Mengkudu	*Morinda citrifolia*	8	44	0,18
7	Bawang Lanang	*Allium Sativus L.*	6	44	0,14
8	Rosela	*Hibiscus sabdariffa*	6	44	0,14
9	Temulawak	*Curcuma zanthorrhiza*	4	44	0,09
10	Kunyit	*Curcuma longa L.*	4	44	0,09
11	Kumis Kucing	*Orthosiphon aristatus*	4	44	0,09
12	Semangka	*Citrullus lanatus*	4	44	0,09
13	Timun	*Cucumidis Folium*	4	44	0,09
14	Biji Mahoni	*Swietenia macrophylla*	3	44	0,07
15	Kelor	*Moringa oleifera L*	3	44	0,07
16	Jahe	*Zingiber officinale*	2	44	0,05
17	Jipang	*Sechium edule*	2	44	0,05
18	Daun Sirsak	Annona muricata L	1	44	0,02
19	Sereh	*Cymbopogon citratus*	1	44	0,02
20	Ketumbar	*Coriandrum sativum*	1	44	0,02
21	Temu Ireng	*Curcuma aeruginosa*	1	44	0,02
22	Pegagan	*Centella asiatica*	1	44	0,02
23	Teh Hijau	*Camellia Sinensis*	1	44	0,02
24	Lidah Buaya	*Aloe vera*	1	44	0,02
25	Cincau	*Cyclea barbata*	1	44	0,02
26	Labu Siam	Sicyos edulis	1	44	0,02
27	Sambiloto	*Andrographis paniculata*	21	44	0,48

***Fidelity* i*Level* (FL) (Recommend)**

FL : Use of each type of simplicia and preference for other types.

Ip : The number of informants who provide information about a particular type of simplicia for a Treatment of certain diseases.

Iu : The total number of informants who delivered all using plant types given.

Table 2. *Fidelity Level* (FL)

No	Plant Name	Spesies	Ip	Iu	FL = (Ip/Iu)x100
1	Seledri	*Apium graveolens L.*	11	44	25,00
2	Sambiloto	*Andrographis paniculata*	8	44	18,18
3	Akar Pule Pandak	*Rauvolfia serpentina*	7	44	15,91
4	Rosela	*Hibiscus sabdariffa*	6	44	13,64
5	Mengkudu	*Morinda citrifolia*	6	44	13,64
6	Daun Salam	*Syzygium polyanthum*	5	44	11,36
7	Timun	*Cucumidis Folium*	4	44	9,09
8	Ciplukan	*Physalis angulata*	4	44	9,09
9	Biji Mahoni	*Swietenia macrophylla*	3	44	6,82
10	Kelor	*Moringa oleifera L*	3	44	6,82
11	Brotowali	*Tinospora cordifolia*	3	44	6,82
12	Temu Mangga	*Curcuma Amada.*	3	44	6,82
13	Kayu Manis	*Cinnamomum zeylanicum*	3	44	6,82
14	Jipang	*Sechium edule*	3	44	6,82

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15	Mahkota dewa	*Phaleria macrocarpa*	2	44	4,55
16	Ketumbar	*Coriandrum sativum*	2	44	4,55
17	Kumis Kucing	*Orthosiphon aristatus*	2	44	4,55
18	Temulawak	*Curcuma zanthorrhiza*	2	44	4,55
19	Semangka	*Citrullus lanatus*	2	44	4,55
20	Bawang Lanang	*Allium Sativus L.*	2	44	4,55
21	Adas Pulo Waras	*Foeniculum vulgare*	1	44	2,27
22	Widara Laut	*Strychnos lucida*	1	44	2,27
23	Kunyit	*Curcuma longa L.*	1	44	2,27
24	Sereh	*Cymbopogon citratus*	1	44	2,27
25	Jahe	*Zingiber officinale*	1	44	2,27
26	Jahe Merah	*Zingiber officanale var rubrum*	1	44	2,27
27	Daun Meniran	*Phyllanthus urinaria L.*	1	44	2,27
28	Pegagan	*Centella asiatica*	1	44	2,27
29	Daun Pepaya	*Carica papaya L.*	1	44	2,27
30	Biji Pala	*Mystrica fragrans*	1	44	2,27
31	Manggis	*Garcinia mangostana L*	1	44	2,27
32	Bawang Putih	*Allium sativum*	1	44	2,27
33	Bawang Dayak	*Eleutherine palmifolia*	1	44	2,27
34	Labu Siam	*Cucurbitaceae*	1	44	2,27
35	Cincau	*Cyclea barbata*	1	44	2,27
36	Belimbing Kuning	*Averrhoa carambola L*	1	44	2,27
37	Daun Sirsak	*Annona muricata L*	1	44	2,27
38	Daun Kenikir	*Cosmos caudatus*	1	44	2,27

Informant Deal Ratio (RKI)

RKI : Representation of the level of agreement among informants regarding the exploitation of medicinal plants

Nur: Referring to the total reports on the use of medicinal plants by all informants

Nt: The number of plant species that fall into one particular category

Table 3. Informant Deal Ratio (RKI)

No	**Plant Name**	**Spesies**	**Nur**	**Nt**	**RKI** $= \frac{(Nur-Nt)}{(Nur-1)}$
1	Sambiloto	*Andrographis paniculata*	14	1	1,00
2	Akar Pule Pandak	*Rauvolfia serpentina*	11	1	1,00
3	Seledri	*Apium graveolens L*	8	1	1,00
4	Mengkudu	*Morinda citrifolia*	7	1	1,00
5	Rosela	*Hibiscus sabdariffa*	6	1	1,00
6	Ciplukan	*Physalis angulata*	6	1	1,00
7	Biji Mahoni	*Swietenia macrophylla*	5	1	1,00
8	Timun	*Cucumidis Folium*	5	1	1,00
9	Daun Salam	*Syzygium polyanthum*	5	1	1,00
10	Bawang Lanang	*Allium Sativus L*	5	1	1,00
11	Kelor	*Moringa oleifera L*	4	1	1,00
12	Jipang	*Sechium edule*	4	1	1,00
13	Kunyit	*Curcuma longa L.*	4	2	0,67

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14	Jahe	*Zingiber officinale*	3	2	0,50
15	Daun Sirsak	*Annona muricata L*	3	1	1,00
16	Kumis Kucing	*Orthosiphon aristatus*	3	1	1,00
17	Kayu Manis	*Cinnamomum zeylanicum*	3	1	1,00
18	Sereh	*Cymbopogon citratus*	2	1	1,00
19	Jahe Merah	*Zingiber officanale var rubrum*	2	2	0,00
20	Daun Kenikir	*Cosmos caudatus*	2	1	1,00
21	Daun Meniran	*Phyllanthus urinaria L*	2	1	1,00
22	Ketumbar	*Coriandrum sativum*	2	1	1,00
23	Pegagan	*Centella asiatica*	2	1	1,00
24	Manggis	*Garcinia mangostana L*	2	1	1,00
25	Mahkota dewa	*Phaleria macrocarpa*	2	1	1,00
26	Temulawak	*Curcuma zanthorrhiza*	2	1	1,00
27	Brotowali	*Tinospora cordifolia*	2	1	1,00
28	Temu Mangga	*Curcuma Amada*	2	2	0,00

Radar Chart Analysis

The percentage of the composition of the active substance will be visible through the simulation of the analysis radar net obtained from the literature study of the parameters of the hypertension mechanism of action, namely total flavonoids, total polyphenols, antioxidants, ACE inhibitors, systolic decrease and diastolic decrease. The use of these six parameters has been shown to have a role in hypertension, which can be seen in the mechanism of action in Figures 1 to 6.

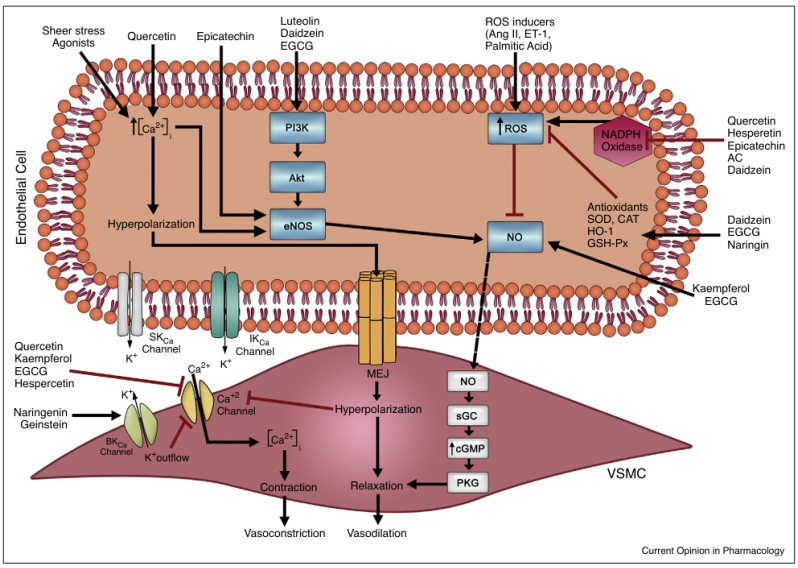

Figure 1. Mechanism of Action of Total Flavonoids in Hypertension (Maaliki et al., 2019)

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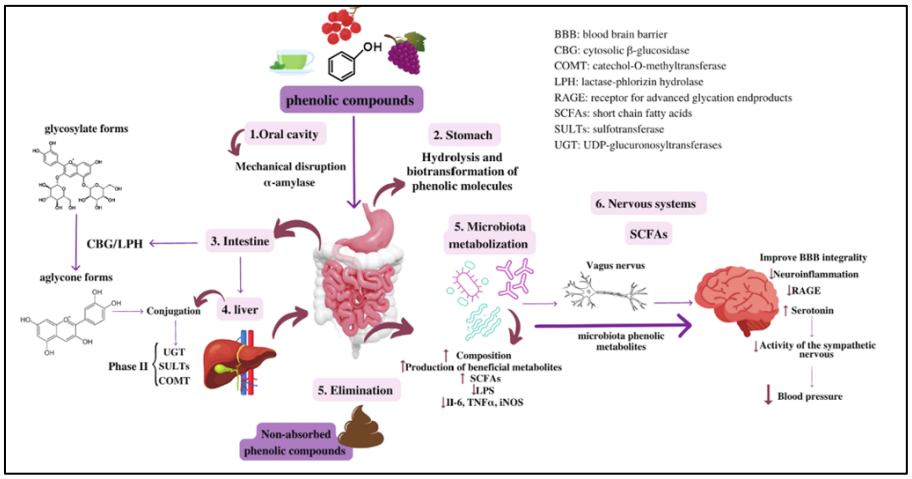

Figure 2. Mechanism of Action of Total Polyphenols in Hypertension(de Brito Alves et al., 2023)

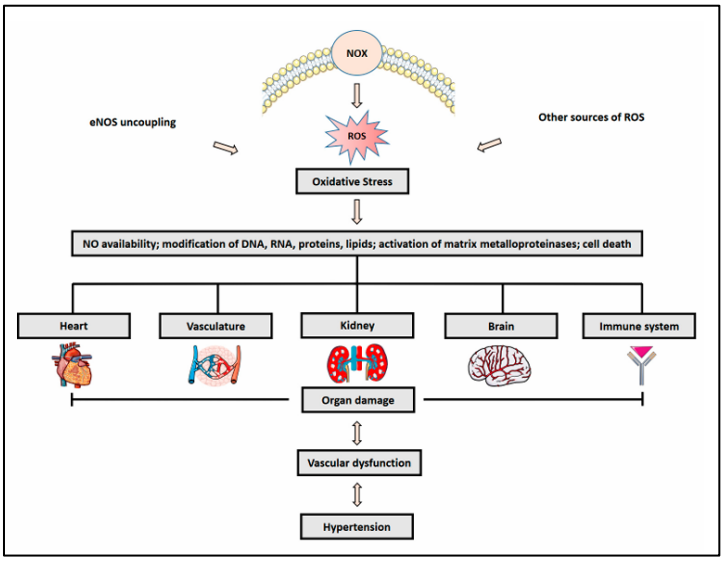

Figure 3. Mechanism of Action of Antioxidants in Hypertension(Amponsah-Offeh et al., 2023)

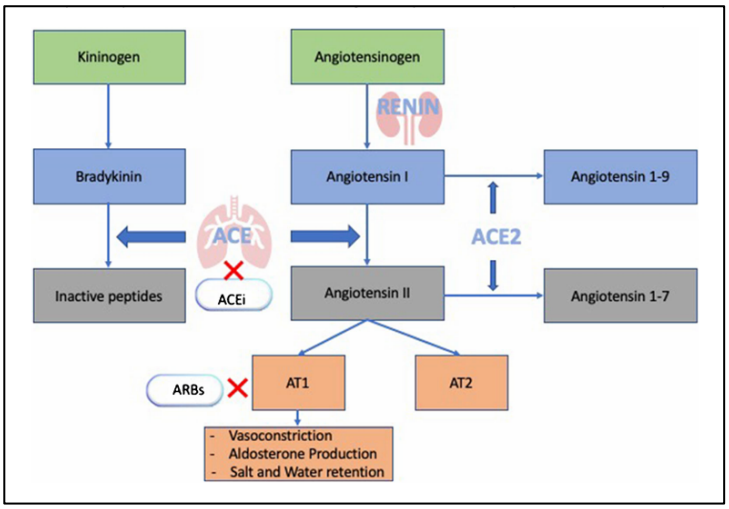

Figure 4. Mechanism of Action of ACE Inhibitors in Hypertension (Turner & Kodali, 2020)

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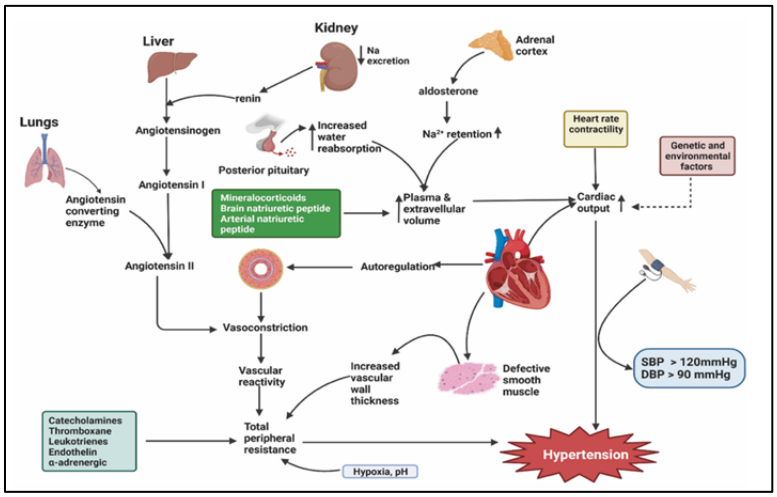

Figure 5. Mechanism of Action of Systolic Reduction in Hypertension (Adua, 2023)

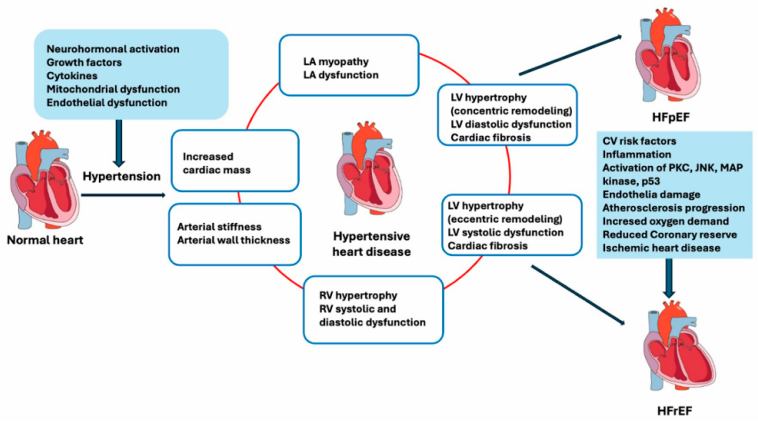

Figure 6. Mechanisms of Action of Systolic Reduction in Hypertension (Gallo & Savoia, 2024)

A literature study of three plants with 6 parameters, namely total flavonoids, total polyphenols, total antioxidants, ACE inhibitors, systolic decrease and diastolic decrease. The highest total flavonoid results were obtained in Sambiloto (*Andrographolis Paniculata*), the highest total polyphenols in Celery (*Apium Graveolens*), the highest antioxidant in Sambiloto (*Andrographolis Paniculata*), the highest ACE inhibitor in Pandak Pule Root (*Rauvolfia Serpentina*), the highest systolic decrease in Pandak Pule Root (*Rauvolfia Serpentina*)), and Diastolic Decline is highest in Sambiloto Pule Root (*Andrographolis Paniculata*). The results of *radar chart analysis* calculations show that the area of the highest is *Andrographis Paniculata*: 766.9, *Rauvolfia Serpentina*: 753.15, and *Apium Graveolens*: 511.2 (Rahayu et al., 2023; Trilestari et al., 2015; Ramonah et al., 2023; Srivastava et al., 2016; Jain et al., 2021; Kholieqoh et al., 2022; W. S. Jung, 2011; Khubaesaroh et al., 2023; Fitrasyah et al., 2021; Rafat et al., 2010; Sukweenadhi et al., 2020; Salleh et al., 2014; Chauhan et al., 2017; Alshahrani et al., 2021; Kooti & Daraei, 2017; Rosaini et al., 2019; Muthia et al., 2017; Adiguna et al., 2023 In, 2024; Touqeer et al., 2022; Ranjini et al., 2015; Jahan et al., 2022; Le et al., 2020; Simaratanamongkol et al., 2014; Sulaiman et al., 2020; Widjajakusuma et al., 2019; Febriana Sulistya Pratiwi., 2022; Lobay, 2015; Ahmad & Rahman, 2022; Oktafiana et al., 2023; Sopian et al., 2024).

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Table 5. Radar Analysis Results

Plant Name	% Polyphenol	% Ace Inhibitor	% systolic decline	% Diastolic Decrease	% Antioxidants	% Flavonoid
Andrographis Paniculata	1,84	48,62	10	11,22	79,96	2,26
Rauvolfia Serpentina	0,242	77,003	13,18	10,07	54,44	0,462
Apium Graveolens	2,756	45,47	8,97	8,023	62,05	1,193

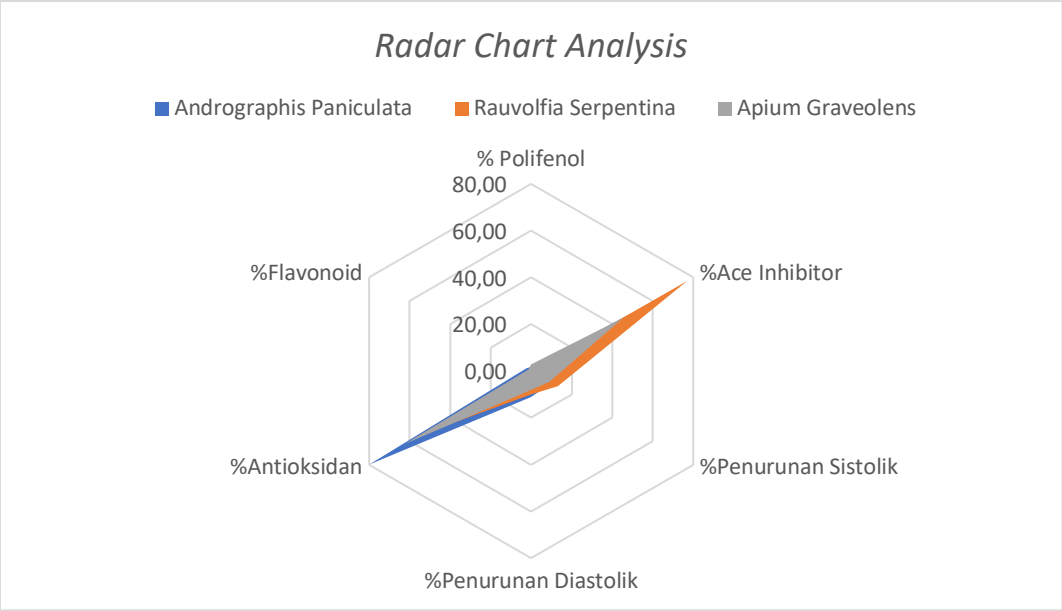

Figure 7. Radar Result

Network Pharmacology

Based on literature studies, the 3 highest compounds were obtained in each plant. In sambiloto (*Andrographis Paniculata*) these compounds are *Andrographolide, Andrographolactone, and Neoandrographolide*. In the Root of Pule Pandak (*Rauvolfia Serpentina*) the compounds *Pinocembrin, Apigenin and Pseudobaptigenin* were found, in Celery (*Apium Graveolens*) *D-Limonene, Myrcene and 4-Terpineol were obtained* (Dwivedi et al., 2021; Kumar et al., 2016; Khanahmadi et al., 2013).

Table 6. Compounds in three selected plants

Plant Name	Compounds	CID
Sambiloto (*Andrographis Paniculata*)	*Andrographolide*	5318517
	Andrographolactone/4-[2-(1,3,6-trimethyl-8,9-dihydro-7H-benzo[7]annulen-2-yl)ethyl]-2H-furan-5-one	44206466
	Neoandrographolide	9848024
Pule Pandak (*Rauvolfia Serpentina*)	*pinocembrin*	68071
	apigenin	5280443
	Pseudobaptigenin	5281805
Seledri (*Apium Graveolens*)	*D-Limonene/Limonene*	440917
	Myrcene	31253

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	4-Terpineol	11230

The total target protein of the three plants amounted to 818 proteins, the potential target protein related to hypertension from *genecards* was obtained 5039 target proteins out of a total of 12366 proteins. In Figure 1.9, it can be seen that there are 302 target proteins from the slice as potential targets of the three selected plants for hypertension therapy.

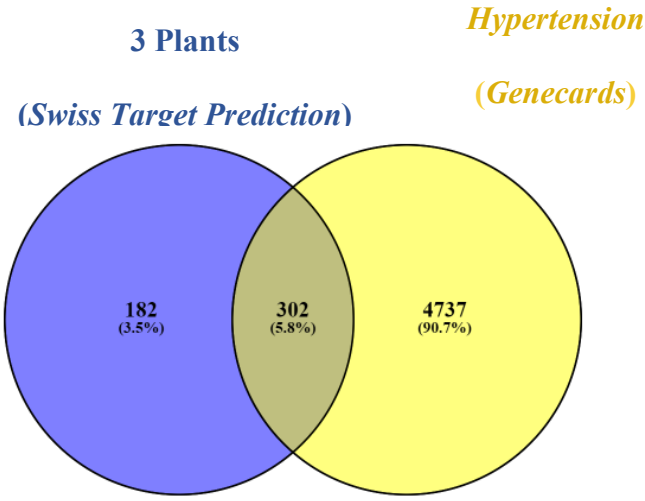

Figure 8. Results Slices of target protein with hypertensive protein

The target protein of the slice is included in the *String* so that a visualization of the interaction between proteins is obtained with a total of 302 nodes, 4831 *edges*, 32 *average node degrees*, 0.497 avg. *local clustering coefficient*, 1967 *expected number of edges*, *and* < 1.0e-16 PPI *enrichment p-value*. In addition, from the 302 *nodes*, 10 main proteins were obtained, namely FLT1, ACE, EDNRA, HSD11B2, CYP11B2, SELE, NR3C2, IL6, TNF, PGF.

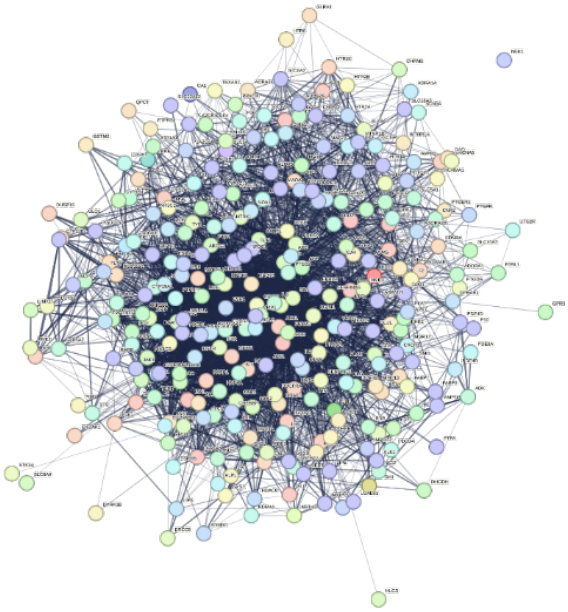

Figure 9. Interactions of key proteins obtained from 302 potential targets

Molecular Docking

This method is used to find out the lowest energy or the best interaction, namely the interaction with the lowest bond energy, the lower the bond energy, the more likely it is to bond. *The 4C2P*

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protein was obtained by entering keywords in the form of enzymes and comparator drugs, namely *ACE Inhibitor* and *Captopril*, from which a validation ligan was obtained in the form of *a native ligand* that attaches to the enzyme receptor structure and functions as a comparator ligand, namely *X8Z709-Captopril.*

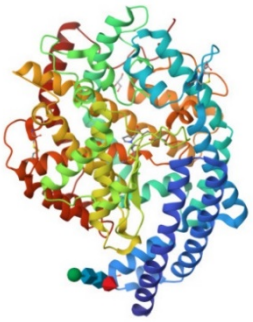

Figure 10.3D Struktur Protein 4C2P

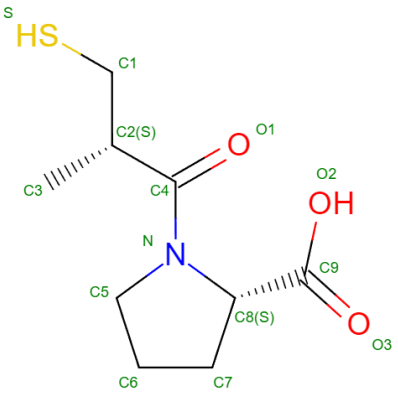

Figure 11. 2D Struktur ligan X8Z Captopril

The native ligan was carried out *a molecular docking* test with 2 treatments to determine the best *affinity* and *RMSD* results, obtaining *affinity* values of -7.28 and RMSD 0.67 (Table 1.7). The ligand X8Z-Captopril has interactions with residues consisting of SER, HIS, GLU, ALA, ZN, TYR, GLN, LYS, and PHE. The interaction can be seen in Figure 3.

Table 7. *Results Moleculer Docking Ligand Native*

Ligand Native (X8Z_Captopril)			
No	**Treatment**	**Affinity**	**RMSD**
1	Without Optimize	-7,28	0,67
2	With Optimize	-6,60	1,25

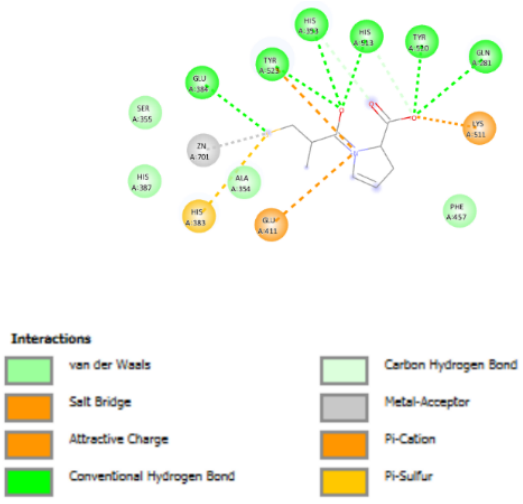

Figure 12. Native Ligand Interactions

Membrane visualization helps to understand whether ligands penetrate or interact with specific parts of the membrane (e.g., hydrophilic or hydrophobic regions). This is useful for predicting how effectively the ligand reaches and binds to receptors embedded in the membrane. The visualization can be seen in Figure 4.

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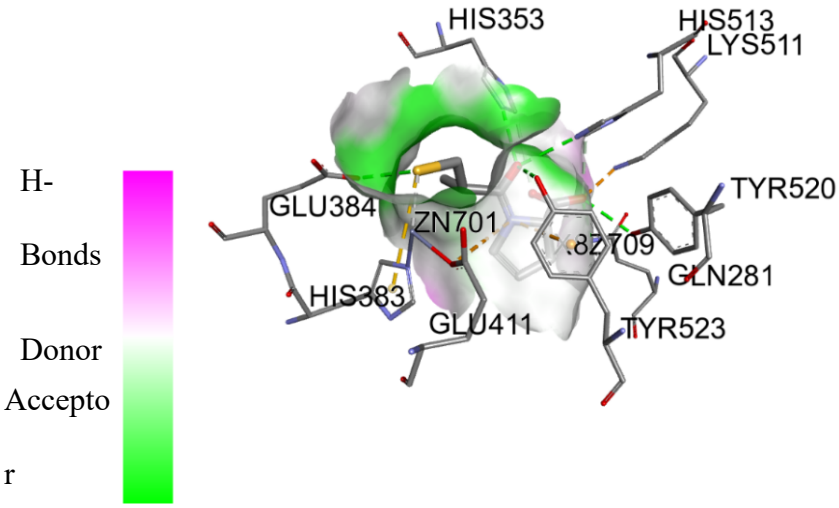

Figure 13. Native X8Z Ligand Cell Membrane

Molecular docking uses test ligands from literature studies of three compounds each on 3 selected plants. Each test ligand must be optimized to optimize ligand interaction and improve ligand geometry. For each test ligand, molecular docking test was conducted to determine the best affinity or interaction. The test results obtained the strongest bond and close to the affinity value of the native ligand, namely the andrographolactone compound of Andrographis paniculata plants with an affinity value of -5.61 (Table 5).

Table 8. *Molecular Docking Ligand Test*

Ligand Uji (Compounds per plant)			
No		**Senyawa**	**Affinity**
1	Sambiloto (*Andrographis paniculata)*	*Andrographolide*	-5,13
		Andrographolactone	-5,61
		Neoandrographolide	-5,43
2	Pule Pandak (*Rauvolfia serpentine)*	*Pinocembrin*	-5,29
		Apigenin	-5,16
		Pseudobaptigenin	-5,32
3	Seledri (*Apium graveolens*)	*D-Limonene*	-4,57
		Myrcene	-3,59
		4-Terpineol	-4,37

Andrographolactone ligand has interactions with amino acid residues consisting of LEU, GLN, ASN, GLU, PRO, ALA, THR, HIS, LYS, VAL, ILE, TRP and MET. In this interaction, it can be seen that there are residues or amino acids that are the same as the native ligands, namely HIS, GLU, ALA and GLN, which can be seen in Figure 5.

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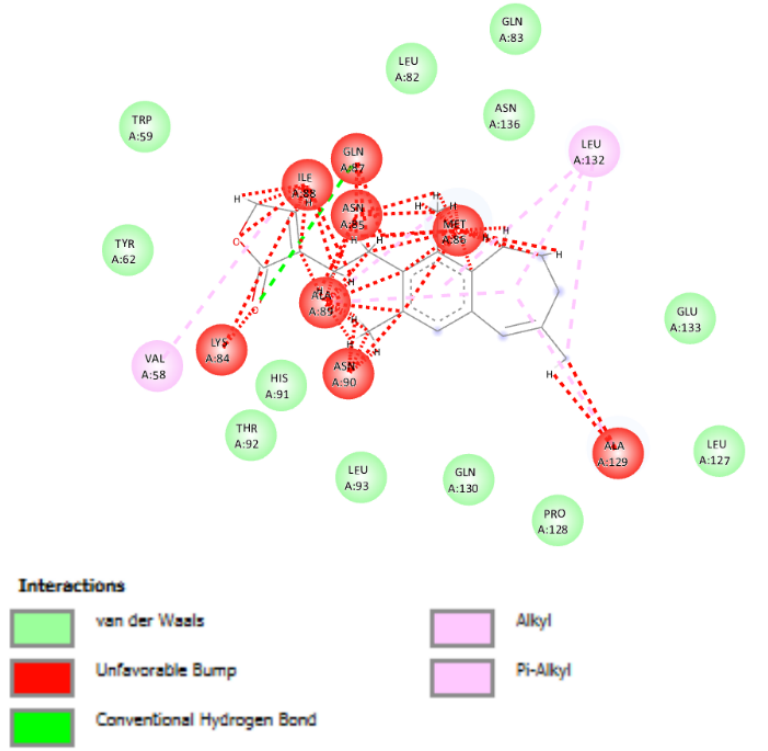

Figure 14. Andrographolactone Test Ligand Interaction

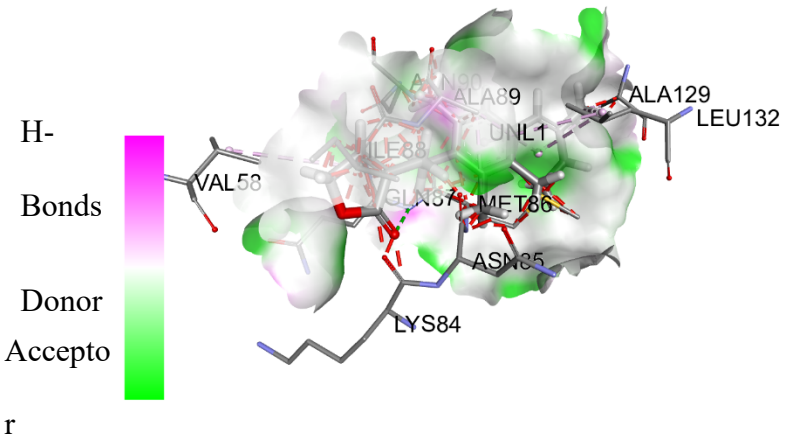

Figure 15. Andrographolactone Cell Membrane

Conclusion

The Ethnomedicine Driven Reversal Approach System (EDRAS) method for the discovery of new drug formulas from natural ingredients effectively and efficiently through ethnomedical studies at the Beringharjo Yogyakarta Jamu Market which has indigenous knowledge obtained 3 most widely used plants, namely Sambiloto (Andrographis Paniculata), Pandak Pule Root (Rauvolfia Serpentina), and Celery (Apium Graveolens) were visualized through radar chart analysis using 6 parameters of anti-hypertension mechanism then explored using network pharmacology, the results obtained 10 main proteins from the active components for hypertension therapy, namely: FLT1, ACE, EDNRA, HSD11B2, CYP11B2, SELE, NR3C2,

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IL6, TNF, PGF. The results of molecular docking confirmed that the smallest affinity is the strongest binding energy in Sambiloto (Andrographis Paniculata) which has an affinity value of Andrographolide (-5.13), Andrographolactone (-5.61), Neoandrographolide (-5.43) with an average affinity (-5.39). The second strongest affinity value was found in Pule Pandak Root (Rauvolfia Serpentina) in Pinocembrin (-5.29), Apigenin (-5.16), Pseudobaptigenin (-5.32) with an average affinity value (-5.25) followed by Celery (Apium Graveolens) in D-Limonene (-4.57), Myrcene (-3.59) and 4-Terpineol (-4.37) with an average affinity value (-4.18). Analysis of the results of ethnomedical studies, Radar Chart Analysis, In Silico (Network Pharmacology and Molecular Docking) found that Sambiloto (Andrographis Paniculata), Pule Pandak root (Raufolvia Serpentina) and Celery (Apium Graveolens) were sequentially confirmed to have the potential to have the main active substances for hypertension therapy. It is important to use the Ethnomedicine Driven Reversal Approach System (EDRAS) method which has been proven to be effective and efficient in terms of time and cost in the discovery of new drug formulas to further prove its safety level using acute toxicity tests.

The study's mention of network pharmacology underscores its relevance; however, the limited discussion might reduce the perceived impact of this methodology. To underscore its importance, network pharmacology should be introduced earlier in the paper, setting the stage for its role in elucidating interactions between plant-derived compounds and biological targets. Presenting network pharmacology as a foundational framework would help to bridge the gap between traditional knowledge and modern pharmacology, emphasizing the scientific validation of traditional medicinal uses.

Furthermore, the connection between ethnopharmacological knowledge and contemporary pharmacological insights could be highlighted more effectively. Traditional healers offer invaluable insights into the therapeutic potential of plants, but these insights benefit from scientific validation through methods like network pharmacology. A structured approach that clearly links the traditional uses of plant compounds to their biochemical interactions in the body revealed via network pharmacology would enhance the research's impact. Without fully integrating these elements, the study may miss a valuable opportunity to demonstrate the relevance and innovative nature of combining traditional knowledge with advanced scientific methodologies.

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